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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,438	12/03/2001	Liming Yu	TNX95-02ABB	8540

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TANOX, INC.
10301 STELLA LINK
HOUSTON, TX 77025

EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,438	YU ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22* is/are pending in the application.

4a) Of the above claim(s) *17 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 -16, and 18-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/27/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 14-16, 18-19 in the reply filed on 01/28/2005 is acknowledged. The traversal is on the ground(s) that the burden of searching for the fusion molecule of interferon alpha or beta with Fc and adding a second molecule to the fusion would not be additional search burden. In view of Applicants argument, the restriction of Groups I-II has been vacated and claims 14-16, and 18-19 would be examined as one Group. Groups III and IV are drawn to an IFN-Fc hybrid molecule comprising an interferon alpha 2a or interferon alpha 2b joined at one end to a chain of an Fc fragment without linker between two molecules further comprising a second interferon molecule joined at its end to the end of other immunoglobulin Fc fragment. Groups III and IV require separate sequence searches for various databases and NPL databases. Searching for groups III and IV would be an undue search for burden on the Examiner. Furthermore, searches for Group III and IV are not coextensive.

Status of Application, Amendments, And/Or Claims

Claims 1-13 are canceled. Claims 14-22 are pending.

Claims 17, 20 -22 are withdrawn from further consideration as being drawn to a nonelected Invention.

Claims 14 -16, and 18-19 are examined on the merit to the extent that they read on the elected invention an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker.

Claim Objections

Claim 19 is objected to as being dependent upon a non elected claim.

Information Disclosure Statement

The information disclosure statement filed 8/27/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the references that are crossed through are not considered.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is noted that a priority of date October 15, 1999 of US Serial No. 09/418734 has been established for all claims drawn to an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker. Review of applications, Serial No. 08/994,719 and 08/719,331 do not reveal support for the "without any linker" limitation. As recited in claims 14-16, 18-19, if applicant disagrees with any rejection set forth in this office action based on examiner's establishment of priority date of October 15, 1999 for the claims drawn to hybrid molecules without peptide linkers in the instantly claimed application Serial Number 10/005,438, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14 -16, and 18-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S.

Patent No. 5,727,125 in view of Peterhans et al (IDS, Analytical Bioch. 163:470-475, 1987).. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims are drawn to a hybrid molecule comprising an interferon molecule joined to its C-terminal end through a peptide linker to the N-terminal of a first gamma immunoglobulin Fc fragment. The instant application claims an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker.

Peterhans et al teach a human interferon alpha2/beta galactosidase hybrid molecule wherein beta galactosidase is fused to the C-terminus of interferon alpha2 establishing the making of functional interferon C-terminal hybrid molecule.

It would have been prima facie obvious to one of ordinary skill in the art to make an interferon/Fc gamma chain fragment hybrid molecule of US Patent 5,727,125 without using a linker as taught by Peterhans et al. One of ordinary skill in the art would have been motivated to make a hybrid IFN-Fc without linker because it is easier to make a direct fusion of proteins as taught by Peterhans et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is indefinite in that it recites acronyms such as ADCC. Use of acronyms results in indefinite language because the acronyms used to define proteins can be

subject to change or reference more than one protein. Therefore, when used for the first time scientific terms should be completely spelled out.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 -16, and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention is drawn to an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker between the interferon and the immunoglobulin Fc fragment, and functional IFN-Fc variants thereof.

To provide undisclosed possession of a claimed invention, the specification must provide sufficient distinguishing identifying characteristics for the invention. The factors to be considered include disclosure of complete functional characteristics, function correlation, method of making an invention, method of treatment, or any combination thereof. The instant application discloses that a linker of different length from one amino acid to16 amino acid can be used to attach the C-terminus of interferon with N-terminus of immunoglobulin Fc. Applicants do not provide a definition of " a variant" or disclose

any IFN-Fc variant, if they had at the time of filing of the instant application. As such IFN-Fc variants encompasses a huge number of substitutions, insertions, deletions, and mutations. Thus, the claims are drawn to a genus of IFN-Fc hybrid.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

As discussed above, the skilled artisan cannot envision the detailed underlying mode of making innumerable variants of IFN-Fc hybrid, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of achieving it.

Claims 14 -16, and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14 -16, and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, were it enabling for an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker between the interferon and the immunoglobulin Fc fragment , would still not reasonably provide enablement for functional IFN-Fc variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how

to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The Nature of Invention: The claimed invention is drawn to genus of IFN-Fc variants.

The state of the prior art and the predictability or lack thereof in the art: The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinants to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions

can tolerate only relatively conservative substitutions or no substitution (see Bowie et.al., 1990, Science 247: 1306-1310, page. 1306, column 2, paragraph2; Wells, 1990, Biochemistry 29:8509-8517).

The amount of direction or guidance present and the presence or absence of working examples: Applicant has provided little or no guidance beyond the mere presentation of an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment with a linker comprising one amino acid or 16 amino acids (see Example II) between the interferon and the immunoglobulin Fc fragment, without undue experimentation, the positions in the protein which are tolerant to change (e.g., by amino acid substations or deletions), and the nature and extent of changes that can be made in these positions. Without any guidance, since innumerable numbers of variants are possible to an IFN-Fc hybrid, It is merely an invitation to the artisan to use the invention as a starting point for further experimentation. Even if a hybrid IFN-Fc variant, was identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that a functional variant must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy function of the protein. Therefore a large number of experimentation would be required to obtain functional variants of IFN-Fc hybrid. Furthermore, once IFN-Fc hybrid variants are obtained, it would require to huge experimentation to evaluate its functionality.

The breadth of the claims and the quantity of experimentation needed: Due to the large quantity of experimentation necessary to generate the indefinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of invention, the state of prior art which establishes unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-16 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landolfi (IDS, U.S. Patent 5, 349,053) in view of Frencke (IDS, EP 467416) or Peterhans et al (IDS, Analytical Bioch. 163:470-475, 1987).

Claims are drawn to an IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker between the interferon and the immunoglobulin Fc fragment and functional IFN-

FC variants wherein (i) gamma-4 chain Fc fragment does not induce ADCC, (ii) the interferon molecule is interferon α2a or interferon α2b and (iii) a composition comprising the hybrid.

Landolfi teaches "chimeric molecules that comprises a portion of a ligand molecule linked to the constant region of an immunoglobulin molecule" (column 4, lines10-13) wherein the Fc region is a human gamma heavy chain (column 6, lines 51-59). Landolfi also examined IgG mediated ADCC and suggests that the antibody dependent cell toxicity (ADCC), resides in the Ig constant region (column 14, lines 64—68). Landolfi does not specifically teach interferon as the ligand although he does contemplate lymphokines, the group of gene which is well known to one of ordinary skill in the art that interferon belongs to. Landolfi teaches a pharmaceutical composition comprising immunoligands for parenteral administration (column 10, lines 1-61)

Frincke et al teach that interferon α –antibody complexes make the IFNα more stable and desirable for in vivo use (column 3 and 4). Neither Landolfi not Frincke et al teach making a hybrid without linker.

Peterhans et al teach a human interferon alpha2/beta galactosidase hybrid molecule wherein beta galactosidase is fused to the C-terminus of interferon alpha2 establishing the making of functional interferon C-terminal hybrid molecule.

It would have been prima facie obvious to one of ordinary skill in the art to substitute interferon/Fc gamma chain fragment hybrid molecule of Landolfi with interferon α of Frincke to make a hybrid molecule that would be more stable for in vivo use because of the recognized stability of hybrid as a preferred use as set forth by

Francke. One of ordinary skill of the art would have been motivated to make a hybrid IFN-Fc without linker because it is easier to make a direct fusion of proteins as taught by Peterhans et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 572-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra
AU 1646
12 April 2005

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600